Chapter 3

Cardiovascular and Cardiorespiratory Function

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Since human spaceflight began in 1961, great emphasis has been placed on studying the effects of weightlessness on cardiovascular and cardiopulmonary function. Because of operational constraints, priority was given in the early piloted missions to telemetric monitoring of the electrocardiogram (ECG), the seismocardiogram (Soviet space program only), respiration, and occasional noninvasive measurements of arterial blood pressure. More extensive in-flight investigations became possible in the early 1970s.

This chapter provides a summary of the known effects of spaceflight on the cardiovascular and cardiopulmonary systems. A brief summary of the hypothesized immediate physiological responses to the spaceflight environment is presented first, followed by a review of evidence for fluid redistribution. The remainder of the chapter consists of available data on aspects of the ensuing adaptive processes, e.g., blood pressures, cardiac dynamics, peripheral circulation, electrical and reflex functions. In-flight observations are discussed first, followed by preflight-to-postflight comparisons; the latter form the majority of the available information. Within each section, results from short flights are presented first, and those from longer flights later; in most cases, this structure also reflects the chronological progression of both the U.S. and Soviet/Russian space programs.

I. Immediate Responses to Spaceflight

The classic hypothesis about the sequence of the immediate physiological responses of the cardiovascular system to weightlessness is presented graphically in Fig. 1. The elimination of gravity-dependent hydrostatic forces causes headward redistribution of body fluid, which then apparently triggers a series of secondary and tertiary cardiovascular and endocrine responses. The endocrine, fluid, and electrolyte responses presumably triggered by increased atrial filling are discussed elsewhere in this volume, but have been included in Fig. 1 to illustrate the hypothesized mechanisms by which a net decrease in total body fluid and plasma volume is established during the first several days of flight.

A. Redistribution of Body Fluid

The first response to elimination of the head-to-foot hydrostatic pressure gradient upon entry into weightlessness is physical: body fluids are redistributed from the legs and lower trunk to the thorax and head until a new steady-state distribution is achieved. Presumably, intravascular fluid shifts first. Changes in regional hemodynamics apparently then cause two transcapillary shifts of fluid, one from the extravascular compartment of the lower body into the blood vessels and the other out of blood vessels into the extravascular compartment of the upper body. A transient negative fluid balance is hypothesized to follow this fluid redistribution.

1. In-Flight Observations

Signs and symptoms related to fluid redistribution reported by American and Soviet crew members include a feeling of fullness in the head (similar to the feeling experienced while hanging upside down on Earth), nasal stuffiness, sinus congestion, rounding and redness of the face (Fig. 2), redness of the sclera and visible nasal and oral mucosa, disappearance of facial wrinkles, puffiness of the eye sockets, engorgement of the veins of the head and neck, and decreased leg girth.[1–12] Some cosmonauts also have reported the sensation of blood flowing or rushing into the head.[3,10,13–15] Eye redness in the Skylab-4 crew gradually cleared, but periorbital and facial edema, facial redness, sinus and nasal congestion, and distention of the veins of the neck and forehead lessened, but never completely disappeared during that 84-day mission.[12]

Infrared photographs (front, back, and side views) taken before, during, and after flight showed that the leg veins of these three crew members were relatively empty in flight, but the jugular veins and veins of the head were always completely full and distended. Transient relief from symptoms was noted for up to two hours after in-flight bicycle exercise. Head fullness was consistently judged to be worse at the end of the day, although one crew member reported transient relief from this symptom after meals. Calf circumference increased by about 1.27 cm during in-flight treadmill exercise but decreased again within 15 to 30 minutes after conclusion of the exercise.

A net loss of body fluid during the first hours or days of weightlessness has been suspected since the early days of spaceflight, on the basis of documented losses of body mass after brief missions. Net losses of body mass after flight ranged from 0.8% to 9.1% of preflight mass in Mercury, Gemini, and Apollo crew members.[16] Available data from Soviet missions indicate an average loss of mass of 2.5 kg (range 0.8 kg to 4.0

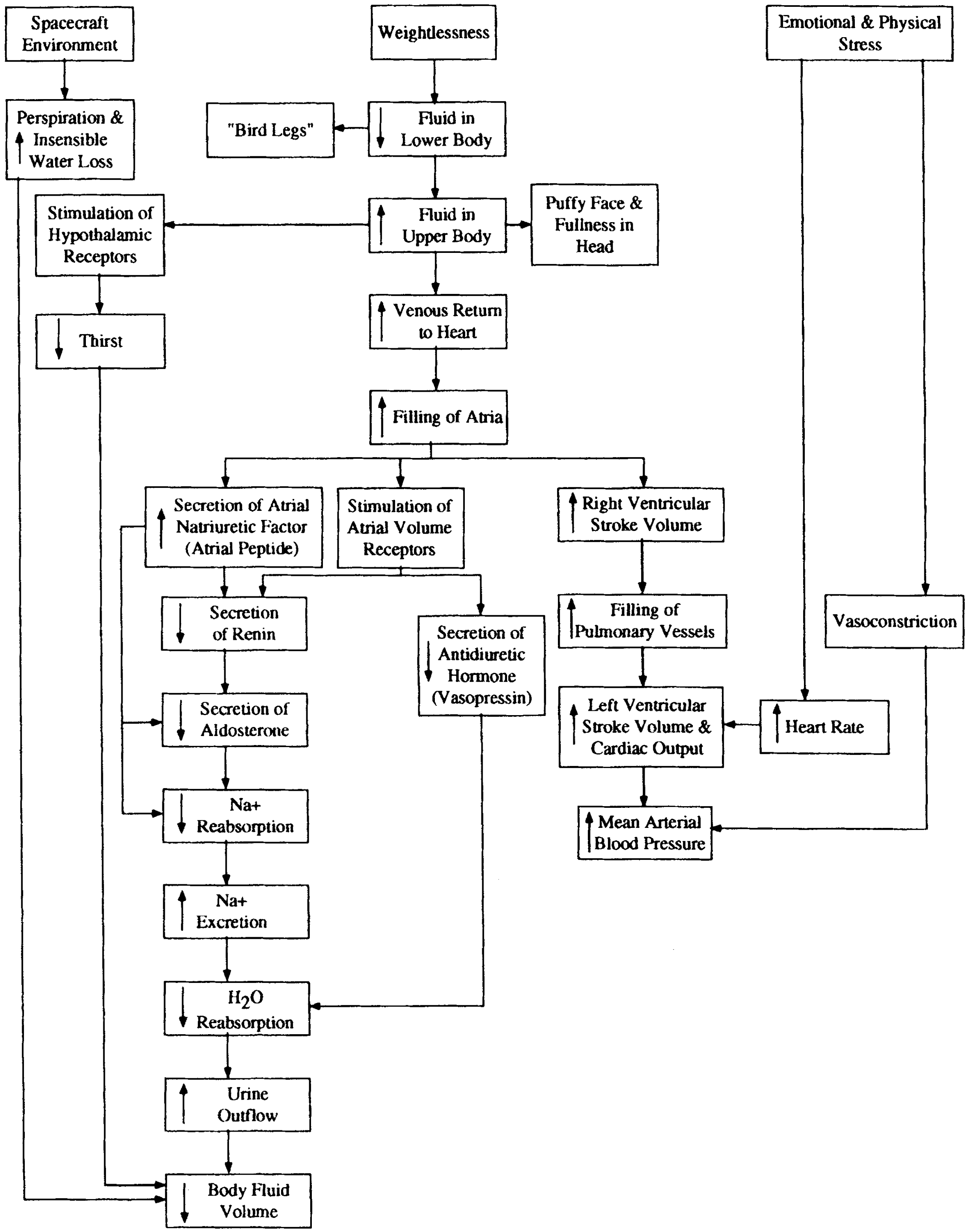

Fig. 1 Hypothesized immediate cardiovascular responses to space flight.

kg) after flight.[9,17–20] The rapid, nearly universal loss of body mass after even brief missions has been interpreted as a loss of body fluid early during flight.

Changes in body mass and leg volume were monitored during Skylab missions (Fig. 3) and during long Salyut missions since 1976 using spring-mass oscillators. Loss of body mass by all Skylab crew members during the first flight days was thought to result from fluid loss.[21] Salyut crew members showed a mean loss of about 0.5 kg by the time the first inflight measurements were taken (no earlier than mission day three).[22–25] Figure 4 depicts changes in mean body mass of American and Soviet crew members.

During the Skylab-4 mission, total leg volume was estimated from several measurements of leg circumference.[8]

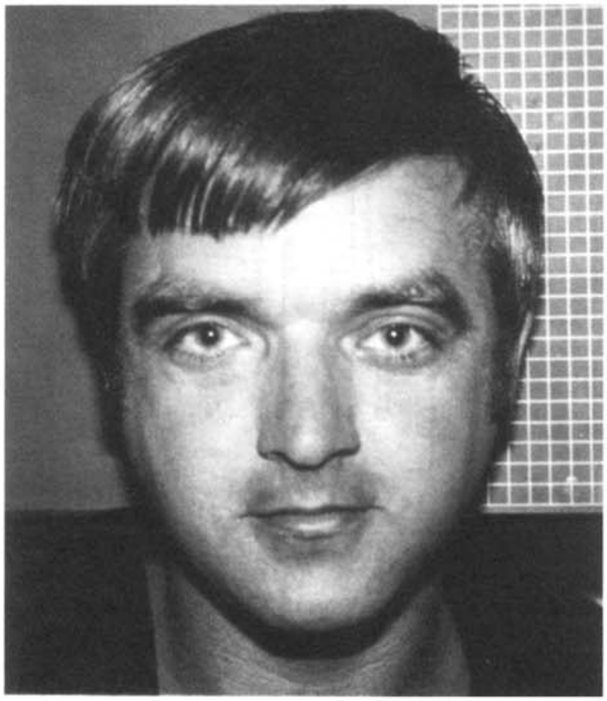

Fig. 2 Rounding and puffiness of the face during space flight.

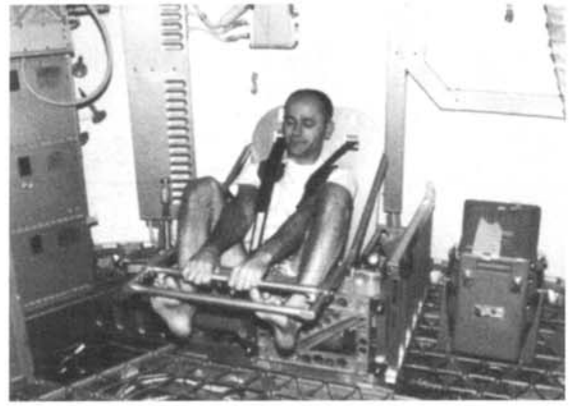

Fig. 3 In-flight photo of Skylab-3 Commander making daily body-mass measurement. The "chair" oscillates along the subject's front-to-back axis; the timer is at the subject's left. The forward elastic pivots can be seen (diagonal braced lightened frame).

Absolute and relative losses from the thigh were much greater than from the lower leg, as shown in Fig. 5. Changes recorded during long Soviet flights closely parallel the lower leg changes observed during Skylab (Fig. 6).[23-25]

Between 1983 and 1985, a stocking plethysmograph (Fig. 7) was used to study the leg volume changes in 11 crew members on five Space Shuttle missions. The average volume reduction in the measured leg during flight for all 11 subjects was 1.026 liters, an 11.6% reduction.[26]

Interpreting leg volume data collected early in flight is complicated by the fact that crew members typically spend some time before liftoff in a characteristic prelaunch position, that is, supine with legs elevated by flexing the hips and knees at 90°. The belief that fluid could begin shifting toward the torso and head on the launch pad is supported by spaceflight experience and by studies of subjects during ground-based simulations. Head-down bed rest studies have shown that the process of headward fluid shifting may take as few as 15 to 30 minutes or as long as two hours, depending on the angle of tilt, posture during the control period, and individual differences.[27] The first in-flight measurement of leg volume probably reflects the combined effects of lying in the prelaunch position plus the initial response to weightlessness.

Segmental bioelectric impedance was used to monitor the fluid shift in four crew members of the U.S.-German Spacelab D-1 mission in 1985.[28] The investigators concluded that most of the fluid had shifted while crew members were in the prelaunch position and that fluid was lost rather than redistributed during that flight.

Some conclusions regarding the magnitude and time course of the headward fluid redistribution can be drawn from these investigations. First, acute exposure to weightlessness results in up to 2 liters of fluid being shifted out of the legs. Second, the fluid shift is distributed unequally between the thigh and the lower leg, with two-thirds of the volume coming from the thigh. Third, most of the fluid shift is completed during the first few hours of weightlessness; however, whether this shift occurs exclusively in space or begins while crew members await launch remains to be established. Fourth, loss of body mass, both in terms of magnitude and time course, corresponds to loss of fluid. Although a shift of fluid out of the legs seems certain, and the fluid presumably first shifts into the torso and then is lost, the route of the fluid loss remains to be established.

2. Postflight Observations

The sensation of fluid moving from the head back toward the feet reported by some crew members immediately after landing[10] supports the expectation that body fluid would be redistributed toward the trunk and lower extremities upon return to Earth. Other evidence of postflight fluid redistribution is offered by measurements of limb volume. The average calf circumference in 24 Apollo crew members 2 to 8 hours after splashdown (all of whom stood or walked during that time) was 1.04 cm (2.8%) less than the last preflight value, a statistically significant difference. The average volume of both legs of six of these crew members after flight was 1005 mL less than their last preflight volumes, also a significant difference.[29-31] Calf circumference and leg volume were still less than preflight values 48 hours after splashdown. During the Apollo-Soyuz Test Project, the lowest leg volumes recorded during flight were taken on the seventh flight day[32]; only about half of preflight leg volume had been restored by 2 hours after splashdown.

Leg volumes immediately after the three Skylab flights were less than those before flight, but returned to near-preflight

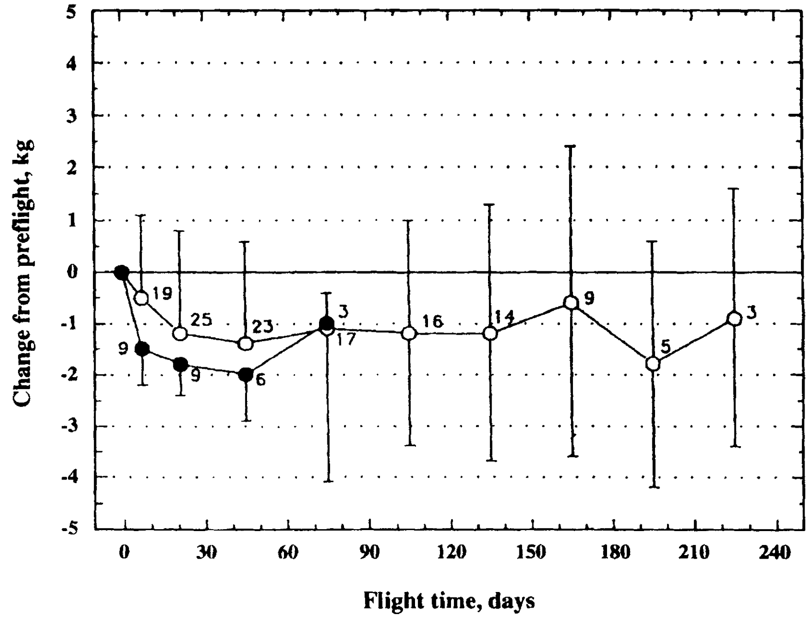

Fig. 4 Change in in-flight body mass of 34 crew members relative to preflight baselines. Open circles, data from Soviet flights (n=25); closed circles, data from U.S. flights (n=9). Numbers next to symbols indicate the number of subjects represented by each point.

levels within several hours of landing.[8] The persistent reduction of calf circumference and limb volume after Apollo flights may have reflected a greater net reduction of body fluid during flight, so that less fluid was available for return to the lower body. Loss of leg tissue also could have contributed. After the Skylab-4 flight, blood distribution in the superficial veins returned promptly to preflight patterns.

Leg volume measured in 10 Space Shuttle crew members 1.5 hours after landing showed a mean decrease of 381 mL (4.3%) per leg from preflight values.[26] Leg volume recovered somewhat over the next 6 days, but was still an average of 283 mL (3.2%) per leg less than preflight baselines. Measurements taken before and after flight were made while the subjects were standing.

Immediately after the 63-day flight on Salyut-4, lower-leg volumes of the two crew members were decreased by 11.7% and 12.0% and were still below preflight volumes by 5.7% and 2.1% one week after landing. Similarly, thigh volumes were decreased by 11.0% and 3.7% on landing day, and in one crew member by 4.0% seven days after landing.[33] In one crew member completing a 175-day flight on Salyut-6, lower-leg volume was decreased by 8.6% six days after landing, but had returned to preflight levels in the other crew members after 9 days on Earth.[34]

B. Central Venous Pressure

The increase in central venous pressure (CVP) (the filling pressure of the heart) produced by the cephalad fluid shift is thought to initiate the early phases of cardiovascular adaptation to weightlessness by stimulating cardiovascular receptors. The end response, as predicted by the theory of Gauer and Henry,[35] is a reduction in plasma volume.

During the Spacelab-1 mission in 1983 and the Spacelab D-1 mission in 1985, Kirsch and colleagues[36,37] tested a premise of the Gauer-Henry hypothesis, specifically, that an increase in CVP preceded the reduced plasma volume observed in virtually all returning astronauts. From 8 days before to 1 day before the 1983 flight, all four crew members experienced a gain in body weight, a fall in hematocrit, and an increase in both central and peripheral venous pressure. (These changes may reflect crew members' activity patterns during the week before launch.) During flight, all pressures were below preflight values; concurrently, hematocrit levels were elevated, suggesting hemoconcentration. CVP was recorded as soon as possible after orbit was attained during the 1985 mission. Again, however, all in-flight pressure readings, even those recorded 20 to 40 minutes after launch, were below preflight values. Subsequent in-flight measurements showed further decreases in venous pressure.

Postflight tests performed one hour after landing revealed CVP to be higher and hematocrit lower than in-flight values, suggesting hemodilution despite the loss of 4% to 9% of body weight during flight. However, by 12 hours after landing, venous pressures had dropped to the lowest levels recorded during this study. Apparently, body fluids that had been stored in the extravascular compartment of the upper body during flight were already being relocated in the first hour after landing, thereby diluting the blood and keeping venous pressure unexpectedly high.

CVP was estimated in Space Shuttle crew members from the intrathoracic (mouth) pressure that transiently interrupted

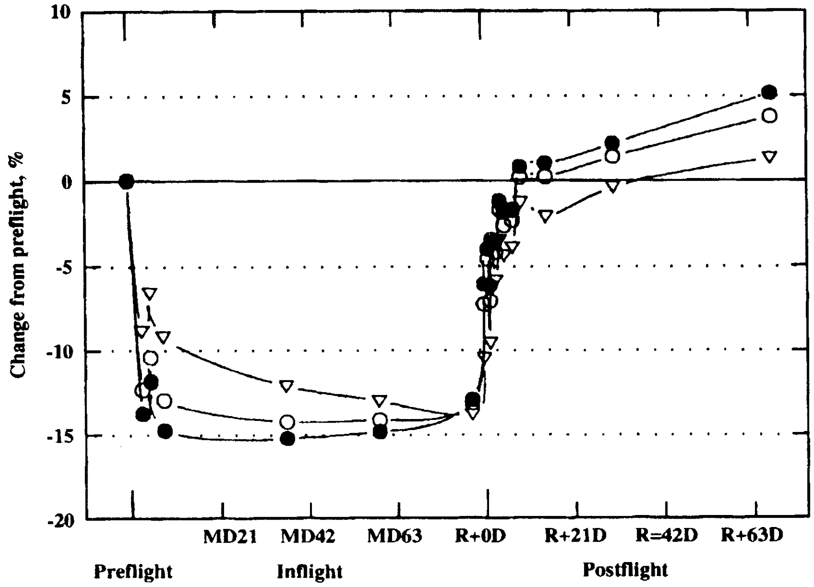

Fig. 5 Change in leg volume of the Skylab-4 crew during flight relative to preflight baselines. Open circles, total leg volume; closed circles, thigh volume; triangles, right leg volume.

jugular venous blood flow[38] (Fig. 8). The results of this study agreed with those of Kirsch et al., despite the use of different measurement techniques. During flight, CVP was consistently lower than before flight; values decreased to a minimum after three days, and then stabilized.[39,40] Verification of this unexpected response of CVP to spaceflight came on the first Spacelab Life Sciences mission (SLS-1) in 1991. CVP was measured invasively with an in-dwelling catheter in the superior vena cava at the level of the right atrium. Except for increases during launch, CVP decreased throughout the measurement period until it reached a value of 0 mm Hg immediately after orbit was achieved.[41]

The failure to detect an increase in CVP early in flight, as predicted by the Gauer-Henry hypothesis for fluid loss, may be attributable to spending up to 2 hours in the previously described prelaunch position. In ground-based studies in which periods of head-down tilt have been preceded by an equilibration period of supine (horizontal) rest, CVP has risen briefly during the equilibration period and then decreased back to supine levels.[27] Thus CVP may peak while crew members await launch, decline before lift-off, and transiently increase only during launch.

Studying CVP early in flight also is complicated by attempts by crew members to avoid an inconvenient diuresis by reducing their fluid intake the day before flight. The diuresis expected early in flight as a consequence of the headward fluid shift has rarely if ever been demonstrated in any astronauts after those who flew in the Mercury Program.

C. Heart Rate

Routine monitoring during the early American and Soviet space programs revealed that heart rates were highest during launch, entry into orbit, extravehicular activity (EVA), and reentry maneuvers.[13,42–45] Gazenko[44] reported that heart rates during the Vostok and Voskhod launches and orbital entries substantially exceeded rates recorded during similar load conditions in a centrifuge before flight, probably because of the emotional stress accompanying actual flight.

1. In-Flight Results

Figure 9 shows the mean resting heart rates of 22 crew members from 1- to 5-day missions flown between 1961 and 1969.[46–50] Kotovskaya's extensive assessment of Salyut-7 crew members[51] revealed heart rates to be 39% higher during the 10-minute prelaunch "ready period" and 52% higher from launch through the first orbit, relative to baseline values obtained one month before flight. Increases in prelaunch heart rate were almost twice as great in cosmonauts making their first flights as in those who had flown previously. In contrast, heart rate responses to reentry were not related to previous flight experience, and sinus tachycardia was more pronounced during reentry than during launch.

During the 1-day Voskhod-1 mission in 1964, the heart rate of one of the crew members was apparently slower during sleep in flight than during sleep before flight.[44] Concurrent atrioventricular conduction also was prolonged, which the authors attributed to increased vagal tone. This tendency for heart rate during sleep to be slower in flight also was demonstrated in Soyuz missions.[13]

In 1982, a French cosmonaut aboard the Soyuz T-6 mission to Salyut-7 recorded elevated heart rates throughout his 8-day flight as he recorded echocardiograms on himself.[52,53] Similarly, during the 7-day STS-51D mission, the average heart rate for four crew members was persistently 15% to 36% higher than supine values recorded before flight. This elevation may reflect the crew members' heightened alertness dur-

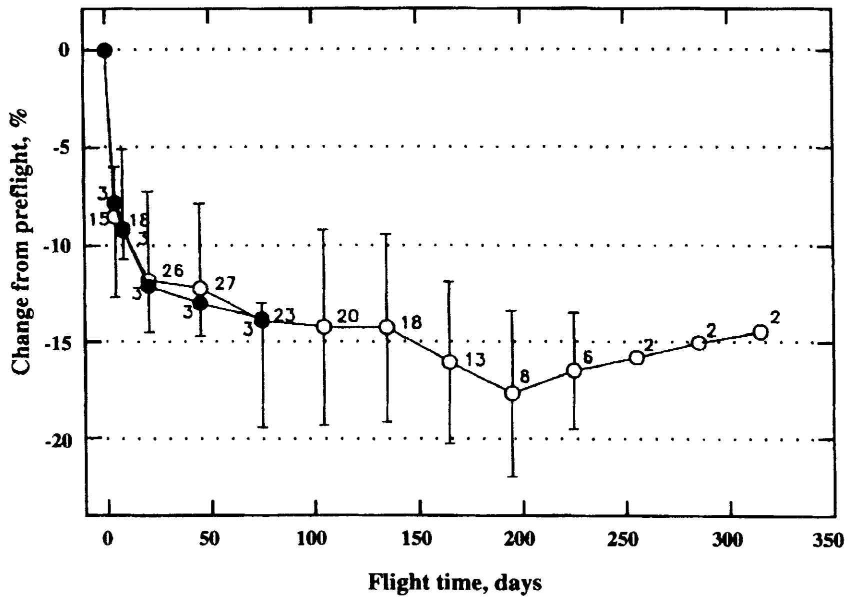

Fig. 6 Change in lower leg volume of 31 crew members during flight relative to preflight baselines. Open circles, data from Soviet flights (n=28); closed circles, data from U.S. flights (n=3). Numbers next to symbols indicate the number of subjects represented by each point.

ing flight in contrast to that on the ground, when they could choose to rest with their eyes closed during testing.

Results from medium-duration flights are somewhat contradictory. In some cases, resting heart rates tended to be somewhat higher than preflight levels,[51,52] but in others, heart rates returned to preflight levels when orbit was attained.[1,54] No correlations with flight duration were apparent.

Some data are available on resting heart rates during long missions. Figure 10 depicts resting heart rates in a group of 26 cosmonauts during missions lasting 30 to 365 days.[24,25,33,55–60] In-flight heart rate seems to be elevated, although much variation exists among individuals. This trend is corroborated by results from the Skylab program, during which all nine crew members showed elevated resting heart rates during flight.[61]

The importance of controlling for the effect of diurnal variation on heart rate was demonstrated during the Gemini Program.[1] Heart rates were clearly slowed during nighttime and sleep periods. Although Berry et al. observed that high heart rates during launch eventually slowed and stabilized during the middle portion of missions (until several revolutions before retrofire), the state of rest, sleep, and wakefulness for these midmission rates apparently was not assessed in relation to similar rest-activity periods on the ground.

The effect of cardiovascular adaptation on resting heart rates in weightlessness remains unclear. Interpretation of the findings described previously is complicated by several factors, the first being the variability of countermeasure protocols. If resting heart rate is to be used as an indicator of the cardiovascular deconditioning that accompanies long exposure to weightlessness, then the type, quantity, and effectiveness of the various countermeasures (particularly exercise) must be taken into account. Second, the conditions for recording "resting" heart rates in a way that accounts for variables as circadian rhythm, prior activity, and level of emotional stress have not been defined. Third, the use of the supine vs standing posture as a preflight reference for resting heart rate remains controversial.

2. *Postflight Results*

The heart rates of the Vostok and Voshkod cosmonauts during reentry and landing exceeded the heart rates during preflight centrifugation tests that simulated the gravitational stress of landing.[62] After 1-day missions, the average heart rate during reentry and landing was 10 beats per minute higher (range 3–22 beats per minute) than that during the preflight centrifuge test. After 3- to 4-day missions, three cosmonauts showed increases of 30–32 beats per minute, and after the 5-day flight, one cosmonaut experienced an increase of 62 beats per minute. However, cosmonauts on the missions lasting 3 to 5 days ejected from the spacecraft for landing, and 5 of the 6 of those on 1-day missions did not eject, so the greater increase in heart rate reflects more than effect of flight duration. Kotovskaya and colleagues[51] have reported that heart rates during reentry were not related to flight duration in Salyut-7 crew members who completed either long-duration or short-duration missions. The finding that tachycardia was more pronounced during reentry than during launch was attributed to cardiovascular deconditioning after exposure to weightlessness and to the emotional tension of the final phase of the flights.

In the U.S. space program, postflight heart rates have been consistently higher than those measured before flight, perhaps

Fig. 7 Space Shuttle crew members taking plethysmograph measurements.

Fig. 8 Space Shuttle crew member estimating central venous pressure during flight.

as a compensatory mechanism for altered orthostatic function. However, emotional stress, dehydration, and the warm temperatures at most U.S. landing sites probably have contributed to the higher rates. After the 9-hour Mercury-8 flight, the pilot's resting heart rate during debriefing on the recovery ship was 22% higher than that during a variety of preflight activities, including launch and centrifuge simulations.[42] The pilot of the 34-hour Mercury-9 flight experienced a 20% higher heart rate on the deck of the recovery ship than he had during preflight simulations and check-out procedures.[63] The heart rates of all Gemini astronauts as they rested after splashdown were 18% to 62% higher than before flight,[2] and heart rates of 24 Apollo astronauts when they were supine were approximately 15% higher after flight than before.[30] After the first four flights of the Space Shuttle, postflight heart rates were 20% greater than preflight rates after the two 2-day missions, 26% greater after the 7-day mission, and 47% greater after the 8-day mission.[64] After the next four Shuttle flights, heart rates were 31% greater than before flight, despite the ingestion of salt tablets and water by the crew members before reentry.[65]

D. Blood Pressure

Among the few in-flight blood-pressure data available from brief flights are 20 blood-pressure measurements obtained throughout the Mercury-8 mission.[42] In relation to preflight values recorded under a variety of circumstances, systolic and pulse pressure were elevated during flight (by about 12% and 50%, respectively), but these values probably were related more to stress than to adaptation to weightlessness during this relatively brief, 9.2-hour flight. Blood pressures after this mission did not deviate substantially from preflight values, but this relative stability apparently was achieved by an increase in heart rate to compensate for a smaller stroke volume.[42] In-flight blood pressures during Mercury 9 were similar to those recorded during preflight simulations and tests; however, the in-flight data were recorded while the crew member rested quietly, in contrast to the ground-based conditions.[63] Both systolic and diastolic pressures were notably lower after the Mercury-9 mission than before, with mean arterial pressure lower by about 24%. However, preflight and postflight blood pressures were not recorded under comparable circumstances, and the effect of dehydration on the postflight values cannot be determined.

Two of the three cosmonauts on the first Voskhod mission apparently experienced a decrease in maximum arterial pressure and an increase in minimum pressure on orbit,[44] thus narrowing the pulse pressure. The highest spaceflight-related blood-pressure measurement to date, 201/90 mm Hg, was recorded from a Gemini astronaut during retrofire; that astronaut's heart rate at that time was 160 beats per minute.

Systolic, diastolic, and mean arterial pressures were measured by auscultation in four crew members during STS-51D. All three pressures were significantly elevated during flight with respect to ground-based measurements made in the supine position. However, the in-flight pressures were not significantly different from preflight standing values.[66]

During the Skylab flights, arterial pressure was measured by auscultation via an automatic system. Most crew members showed elevated resting systolic and pulse pressures and decreased diastolic and mean pressures, although not always to a statistically significant degree.[61] Blood pressure data also are available from 17 crew members on 49- to 326-day Salyut and Mir missions (Fig. 11). Resting mean arterial pressure (MAP) recorded by oscillometry remained essentially unchanged during flight.[24,59,67–71]

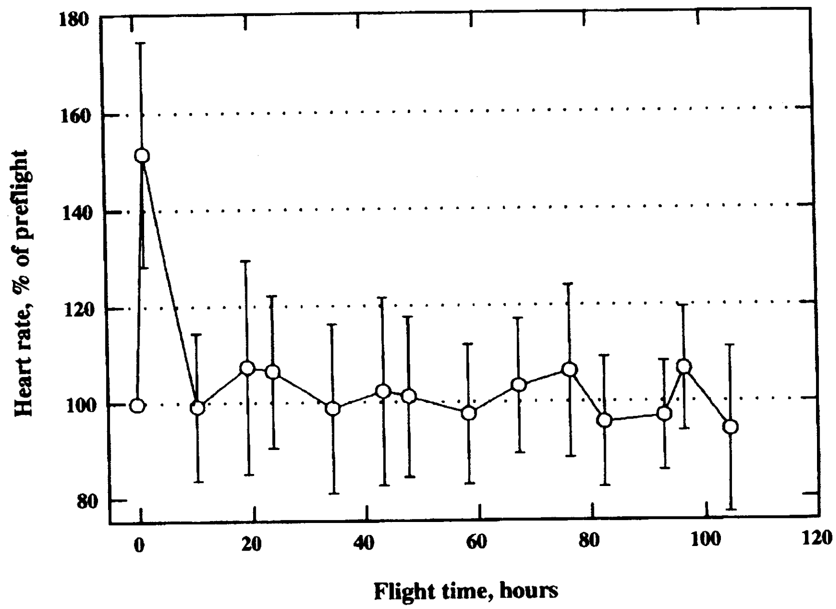

Fig. 9 Change in resting heart rate in 22 cosmonauts during 1- to 5-day flights relative to preflight baselines.

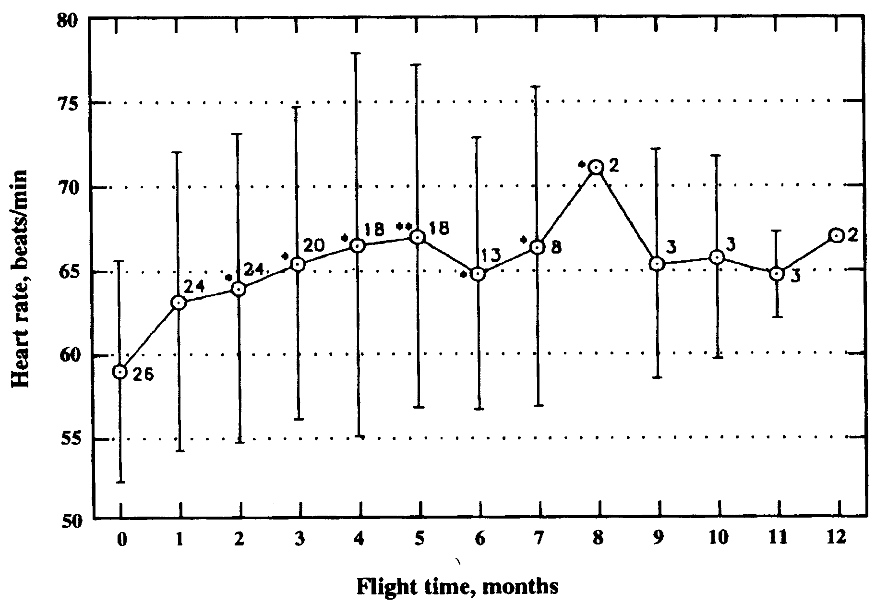

Fig. 10 Mean resting heart rates of 26 crew members during 30- to 365-day flights. Numbers next to symbols indicate the number of subjects represented by each point. *Significantly different from before flight, P<0.05 or **P<0.01.

II. Cardiac Dynamics

At the level of the heart, the headward fluid shift would be expected to produce a transient increase in stroke volume and cardiac output as a result of the short-lived increase in central blood volume and ventricular diastolic filling. These changes should temporarily increase arterial pressure, producing a reflex slowing of the heart and decreased peripheral resistance. Because few subjects have been studied to date, and because most evaluations of cardiac function have taken place before and after rather than during flight, testing for statistical significance has little value for summarizing available data. A more appropriate approach is to identify consistencies and inconsistencies in the direction of changes in cardiac dynamics in relation to flight day.

Preflight and postflight studies in the U.S. and Soviet space programs have included measurements of cardiothoracic ratio, systolic time intervals, echocardiography, rheography, and vectorcardiography. Systolic time intervals, measured during rest and lower-body negative-pressure (LBNP) stress, were used to assess changes in ventricular function after the Skylab-4 mission. Postflight increases in the ratio of pre-ejection pe-

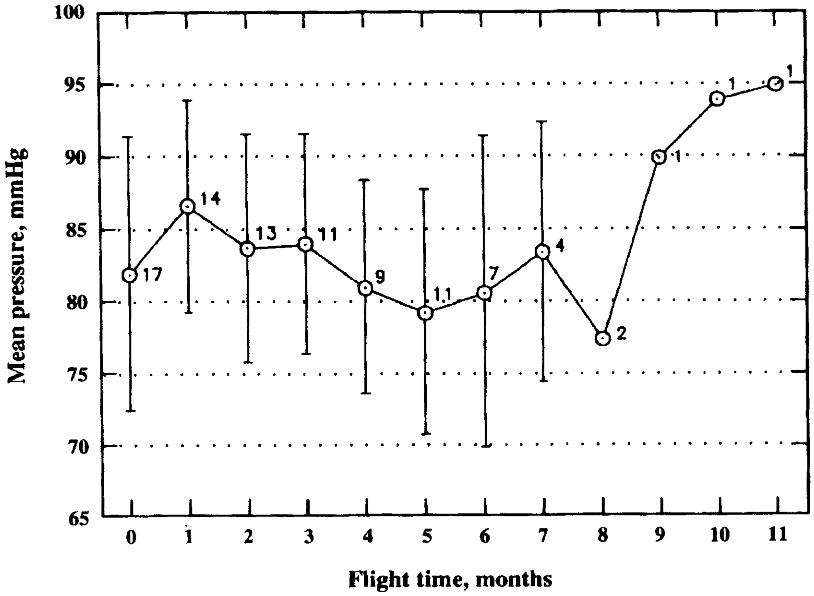

Fig. 11 Mean resting arterial pressure, measured by oscillometry, in 17 crew members during 49- to 326-day flights. Numbers next to symbols indicate the number of subjects represented by each point.

riod to left ventricular ejection time (PEP/ET) from baseline values taken before flight paralleled the marked decrease in ventricular filling and diminished total blood volume. However, a decrease in contractility could not be excluded as a contributor to the increase in PEP/ET.[31,72]

A. Echocardiography

The use of echocardiography to assess cardiac dynamics during flight has been based on the need for noninvasive techniques as well as the limited stowage space available aboard spacecraft. Although the ultrasound devices used have not been identical, all have had two-dimensional and M-mode imaging capabilities.

1. In-Flight Studies

The earliest in-flight echocardiograms were collected 3, 4, and 9 hours after launch from three crew members on the STS-51D and -51G missions.[73] Control measurements also were taken before STS-51D while the crew members were supine and standing. Relative to standing preflight values, left-ventricular end-diastolic volume (LVEDV), stroke volume (SV), cardiac output, and stroke work were elevated on the first flight day, but then fell below baseline for the remainder of the flight. A Soviet-French study of one crew member on Salyut-7 seemed anomalous in many respects, particularly the steadily increasing cardiac output that peaked on the fourth flight day with a sustained increase in LVEDV not seen in any other subjects.[74] No evidence of a decrement in myocardial contractility, assessed by velocity of circumferential fiber shortening and maximum systolic ejection rate, was found in any echocardiographic study conducted during brief missions. Rate-pressure product (the product of heart rate and systolic blood pressure) was used as an index of myocardial work and oxygen demand for STS-51D and was elevated on several inflight days.

Early Soviet studies of stroke volume and cardiac output used impedance cardiography, a technique that measures variations in local electrical resistance during the cardiac cycle.[75] Arterial pressure by oscillometry and heart rate by ECG were usually recorded simultaneously. The mean resting heart rate, MAP, SV, and cardiac output of 13 cosmonauts are shown in Fig. 12.[19,67–69,76–78] None of the mean in-flight values differed significantly from preflight values, although much variability, particularly in cardiac output, was noted within subjects.

The three cosmonauts aboard the 8-month Soyuz T-10 mission to Salyut-7 in 1984 recorded their resting echocardiograms at the end of each month in flight.[79] Two of the three cosmonauts maintained reduced LVEDV (14% and 19%) and reduced SV (15% and 12%) on orbit with heart rates that were 10–12 beats per minute higher than the preflight baseline.

2. Preflight-to-Postflight Comparisons

Henry and others[80] recorded resting M-mode echocardiograms from three astronauts before and after Skylab-4. Relative to preflight data, resting LVEDV and SV were reduced immediately after flight. Volume reductions were greatest in the two crew members who had the largest values before flight, and changes persisted for more than 10 days after flight in these two crew members.

Bungo and others[65] studied 17 crew members before and after STS-5 through STS-8, all 5- to 6-day missions. All crew members ingested salt tablets and water equivalent to 1 liter of isotonic saline during the hour before entry and landing.

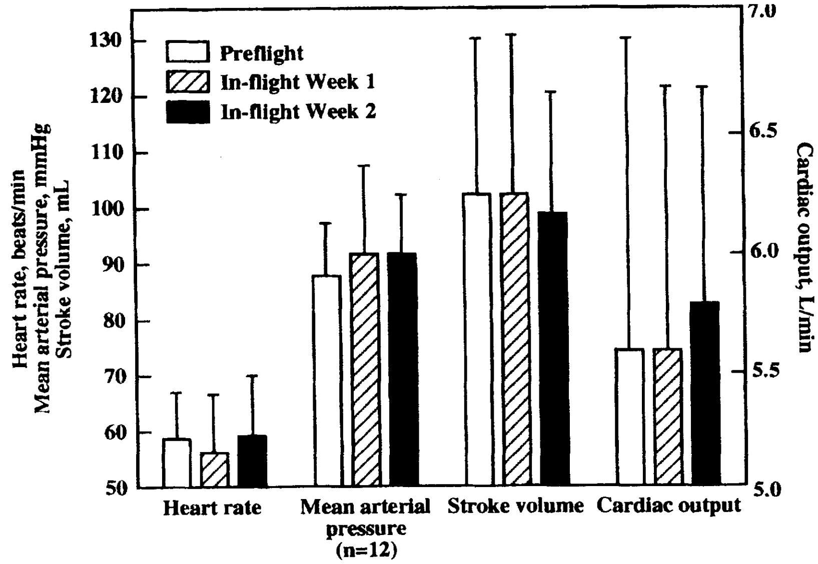

Fig. 12 Resting heart rate, mean arterial pressure, stroke volume, and cardiac output in 13 crew members before and during flight.

At landing, LVEDV and SV indexes and stroke work were significantly less than preflight values (23%, 29%, and 22%, respectively), while heart rate, MAP, and systemic vascular resistance were significantly elevated (31%, 11%, and 31%, respectively).

No significant differences were detected in LVEDV index, cardiac index, fractional shortening, or ejection fraction. By 7–14 days after landing, the total group of 17 crew members had significantly smaller LVEDV and end-systolic volume indexes (10% and 22%, respectively) and significantly higher heart rate (7%), ejection fraction (7%), and fractional shortening (11%) relative to preflight values. Stroke volume, cardiac index, stroke work, MAP, and systemic vascular resistance did not differ significantly from the preflight values.

In a subsequent report, Charles and Bungo[81] reevaluated these data along with the data from two crew members of STS-41B and STS-41D. The six subjects with the smallest LVEDV and SV indexes before flight were compared with the six with the largest. Only the latter subgroup showed significantly reduced LVEDV and SV after flight. However, heart rate and MAP were significantly elevated in both subgroups after flight. Both before and after flight, total peripheral resistance (TPR) was significantly greater in the subgroup with the smallest initial LVEDV and SV indexes.

Preflight and postflight echocardiograms have been routine for long Soviet missions to the Salyut and Mir space stations since 1978. Atkov and others[79] reported decreases in left ventricular end-diastolic, end-systolic, and stroke volumes one day after landing in 15 cosmonauts studied at rest before and after long missions. Three of these 15 cosmonauts recorded resting echocardiograms monthly during their 8-month mission as well. Although one experienced elevated resting end-diastolic and stroke volumes during flight, the stroke volumes of all three were below the preflight baseline immediately after landing. Moreover, the heart-rate response of these three cosmonauts during LBNP was greater after the flight.

B. Electrophysiology

Early in both the U.S. and Soviet space programs, electrocardiograms were monitored routinely and down-linked via telemetry during missions.[82] As flight durations increased and it was realized that weightlessness posed no immediate danger to the crew members' health, ECG monitoring became limited to the more stressful phases of flight, e.g., launch and orbital insertion, docking maneuvers, EVAs, physiological stress testing, and reentry and landing. Table 1 summarizes the cardiac dysrhythmias that have been observed in the U.S. space program.

1. U.S. Results

During brief Gemini missions, phonocardiography was used to observe the relationship between the Q-wave and the onset of mechanical systole.[1,2] The investigators concluded that the duration of electromechanical systole correlated closely with heart rate. Stable values were observed for electromechanical delay (onset of ventricular activation to onset of first heart sound), with shorter values during peak heart rates at launch, reentry, and during EVA. The only dysrhythmias of note were infrequent, premature atrial contractions (PACs) and premature ventricular contractions (PVCs).

One brief episode of atrial bigeminy was noted during a strenuous lunar-surface EVA in the Apollo program. Although heart rates on the lunar surface were not excessive (up to 160 beats per minute), both Apollo-15 crew members developed cardiac dysrhythmias on the lunar surface and again during

Table 1 Summary of spaceflight-related cardiac dysrhythmias

Program	During Launch	During Flight	During Extravehicular Activity	During Entry or Landing	After Flight
Mercury	Rare PACs, PVCs during prelaunch activities	More pronounced sinus dysrhythmia One PAC, one PVC, one fusion beat			
Gemini		Rare PACs, PACs			
Apollo		On lunar surface: PVCs, PACs during normal flight, sleep, and awakening, and after return to lunar surface	Lunar-surface EVA: atrial bigeminal rhythm with extreme fatigue		
Skylab		PVCs during normal flight and exercise; AV block during LBNP recovery; ectopic beats, especially during LBNP; AV junctional rhythm at rest and after LBNP; ST segment and T wave changes during maximum stress; ventricular couplet, 3-beat ventricular tachycardia during exercise			Ventricular tachycardia
Space Shuttle	PVCs, PACs		PVCs, PACs, sustained ventricular bigeminy, blocked P waves	PVCs, PACs	

their return to Earth. Pestov and Gerathewohl[83] interpreted the occurrence of these dysrhythmias as evidence that the two crew members were drawing heavily on their physiological reserves in relation to the excessive work loads, and considered the dysrhythmias anomalous. The crew showed a marked potassium deficiency that apparently contributed to the dysrhythmias.

In the Space Shuttle Program, ECG was monitored continuously only during the first four test flights; thereafter, ECG was recorded only during EVAs. During the Space Shuttle test flights, frequent PVCs were observed in two crew members during entry and landing. Approximately one third of Shuttle crew members performing EVAs exhibited either PACs or PVCs during those activities: One showed sustained ventricular bigeminy for about 10 minutes, and another had episodes of frequent PACs. The etiology of these dysrhythmias is unclear, but the performance of physically stressful work in a 100% oxygen hypobaric environment may have been a contributing factor.

Vectorcardiography also has been used to study cardiac electrophysiology during space flight. During Skylab, one common observation was an increase in the QRS maximum vector, attributed to the headward fluid redistribution.[84] The duration of the P–R interval, which provides an estimate of atrioventricular conduction time, also was noted to increase during flight. This change may have resulted from increased vagal tone.[84,85]

2. Soviet/Russian Results

Romanov and others[86] have summarized observations of cardiac function in 21 cosmonauts on 42 brief and long missions between 1964 and 1985. During the longer flights, ECGs were collected every 2 to 3 weeks at rest, during exercise periods, during LBNP testing, and also during EVA. During launch and orbital insertion, tachycardia (presumably sinus) was noted in all crew members, but was not included in the authors' overall assessment of dysrhythmias. The most common in-flight dysrhythmias in this group were extrasystoles, with supraventricular types being more common than ventricular. The overall frequency of extrasystoles was highest during orbital insertion and the first few orbits; the authors attributed this finding to an unspecified acute response to weightlessness. Eleven cosmonauts exhibited a 10–25% decrease in R wave and S wave amplitudes, and a 25–50% decrease in T wave amplitude, beginning 2 to 3 months into flight. None of these changes was described as pathological, and the authors attributed them to alterations in hemodynamics, fluid-electrolyte metabolism, and microcirculation.

On the first postflight day, most of this group of cosmonauts exhibited sinus tachycardia, with corresponding increases in P wave amplitude and decreases in QRS complex and T wave amplitudes. One crew member exhibited an ST segment shift to 0.2 mV immediately after flight, and two displayed increased right ventricular activity, apparently due to anterior rotation of the right ventricle. Two other crew members presented signs of increased left-ventricular electrical activity 2 weeks after flight, coinciding with an increase in motor activity. Some of the ECG changes observed during the longer flights persisted for a variable time after flight. However, all ECG changes returned to normal by 1 to 2.5 months after long missions, and within 1 to 2 weeks after brief missions.

In another study, 24-hour Holter monitoring of two cosmonauts who completed a 1-year flight revealed labile heart rates after landing, ranging from 74 beats per minute to 128 beats per minute in one crew member and from 70 beats per minute to 178 beats per minute in the other. Both displayed diffuse, decreased T wave amplitudes and an increase in the QRS/T amplitude ratio immediately after return to Earth, but these indexes returned tonormal within 2 to 4 days. The two cosmonauts displayed 12 and 15 isolated ventricular extrasystoles during the first 24 hours after landing.[25]

III. Peripheral Circulation

Assessing the response of the peripheral circulatory system to space flight is difficult because of technical difficulties associated with using noninvasive techniques to obtain the necessary measurements. Critical measurements include arterial and venous pressures and volumes. Investigators have had to rely on indirect assessments of regional volumes or changes in volume, and have only rarely obtained direct measurements of vascular pressure. In most instances, hemodynamic measurements have been limited to volume changes of whole limbs and estimates of blood flow or vascular pressures in large vessels obtained with ultrasound, impedance, or pulsographic methods.

A. Arterial Responses to Weightlessness and Return to Earth

The arterial system is not greatly influenced by direct hydrostatic effects, but it is very sensitive to reflex stimuli arising from changes in blood distribution. Arterial vasoconstrictor tone may decrease early during flight in response to the cepahalad fluid shift, which stimulates cardiovascular and sinoaortic baroreceptors. Adaptation to space flight may involve modification of cardiovascular baroreflex functions, a change in the sensitivity of the arterioles to neurohumoral stimulation, or both.

The primary arterial response to weightlessness results from the redistribution of fluid from the lower to the upper body during the initial hours of weightlessness. Predicted secondary responses, namely increased blood flow and pressure in the thorax and head coupled with decreases in the lower body regions, were supported by data collected during the Salyut-6 and -7 missions.[87,88] Pulse filling of forearm vessels increased by 22% and that of the calf decreased by 29% during flight. The tone of large arteries in the upper and lower body (as derived from impedance waveforms) declined, with the larger decrease in the calf.

The initial increase in central blood volume upon exposure to weightlessness would be expected to stimulate cardiopulmonary volume receptors. One reflex response would be a decrease in peripheral vascular tone, which would redistribute fluid to the periphery and reduce central blood volume. According to this hypothesis, then, both peripheral vascular tone and TPR would decline during the first few days of flight. TPR was calculated for four crew members on STS-51D from the ratio of MAP (obtained by sphygmomanometry) to cardiac output (obtained by echocardiography). Although TPR seemed to decrease on the first flight day relative to preflight measurements (both standing and supine), this trend was not statistically significant.

During Salyut-7, arterial tone was estimated indirectly from ultrasound determinations of the propagation time of pressure waves in the aorta and iliac arteries; a decrease in transit time was interpreted as an increase in arterial tone.[52] Pressure-wave transit time in the aorta was not altered during flight; however, that of the iliac arteries decreased and did not return to control values until 3 days after return to Earth. The authors suggested that this unexpected result may reflect an important adaptive change in the circulation involving an increase in peripheral resistance or an increase in muscular tone of the lower limbs (not measured) later in flight. Postflight results collected on landing day indicated increases in femoral-artery blood flow and decreases in pulse-wave transit time in the tibial and femoral arteries. The former finding was interpreted as representing difficulties in arterial vasomotor control, and the latter, which did not return to preflight levels until the third recovery day, as an increase in arterial compliance.

Femoral blood flow and changes in TPR, measured with the same ultrasound device as that used on Salyut-7, were not consistent for two crew members on STS-51G.[74] One had increased femoral blood flow and decreased TPR, suggesting vasomotor deconditioning. This crew member also experienced hypotensive blood-pressure responses to thigh occlusion and to standing after landing. In contrast, the other crew member's femoral blood flow decreased moderately and his TPR increased during the flight. This crew member readapted well upon return to Earth. The pressure-wave propagation time along the aorta and in the arteries of the leg were used to estimate arterial tone in this study as well. The crew member who had orthostatic difficulties after flight had an increase in aortic and lower-limb compliance (propagation time increased), and the crew member who adapted well after flight had a decrease in aortic and limb compliance during flight. Pourcelot and colleagues[89] noted the differences in individual responses in the peripheral circulation during spaceflight and called for other experiments to correlate these circulatory changes with results of neurohormonal regulation.

Leg blood flow was measured during the Skylab-4 mission as an indicator of lower-body arterial tone.[90] Although the in-flight results varied greatly, leg blood flow was increased in all three crew members throughout most of the 84-day flight, suggesting persistent relaxation of lower-body arterial tone. Leg blood flow reverted to preflight levels by the time of the first postflight measurement on the day of landing, suggesting that arterial tone recovers rapidly after re-exposure to gravity.

During the long Salyut-6 and -7 missions, forearm pulse filling first increased and then returned to preflight levels, while that of the calf decreased and remained decreased throughout the flights.[87,88] The decrease in calf pulse filling may reflect changes in the contractile tension of the leg muscles; however, pulse blood filling was significantly different in the arm and leg vessels before flight: Forearm vessels typically had higher tone in small caliber vessels, while leg vessels had higher tone in larger vessels. Exposure to weightlessness, however, tended to reduce such differences.[87,88]

During 160- to 326-day Mir missions, Yuganov et al. (personal communication) noted decreased tone of vessels in the arms (particularly in small peripheral vessels), and decreased pulse filling and increased tone of the vessels (particularly large vessels) of the legs. The reason for the observed increase in large vessel tone in the leg remains unexplained.

B. Venous Response to Weightlessness and Return to Earth

Unlike the arterial system, the venous vasculature is greatly influenced by hydrostatic pressures associated with gravity and is only weakly modified by neural reflex stimuli. In the normal upright posture, approximately 75% of the total blood volume is below the level of the heart.[91] The initial response to removal of the hydrostatic gradient is the redistribution of approximately 2000 mL of blood to the upper body, mostly to the compliant, low-pressure vascular regions of the pulmonary circulation, right heart, and systemic veins. The ensuing change in venous compliance would produce large changes in blood distribution, venous return, and cardiac filling. Increased venous compliance during space flight would impair orthostatic tolerance upon return to Earth by allowing greater quantities of blood to pool in the lower body.

Both American and Soviet investigators have used changes in leg or arm circumference to estimate venous compliance. The assumption is that during any sudden change in transvascular pressure, whether imposed by a sudden change in posture, limb occlusion, or LBNP, most of the translocated blood is moved to the large veins. The relation between changes in transmural pressure and changes in limb volume can then be used to estimate venous compliance. This assumption was supported by data from a ground-based study[92] in which magnetic resonance imaging was used with conventional limb plethysmography to estimate changes in venous pooling during thigh-cuff occlusion at pressures ranging from 20 to 100 mm Hg. At 40 mm Hg, 90.2% of the pooled blood was located in the deep leg veins. Estimates of venous responses to weightlessness or to provocative stimuli before and after spaceflights are described below.

1. In-Flight Results

Pulsograms and venous-pressure estimates were obtained from cosmonauts on a 63-day Salyut-4 mission.[11] Pulse fluctuations of the jugular veins were obtained concurrently with the carotid arterial pulse to obtain venous-arterial pulsograms (VAPs). On flight days 8 through 13, the changes in VAP tracings from two cosmonauts indicated increased filling of the jugular vein; jugular pressure was estimated to be 50–67% higher than before flight. After 43 to 44 days, however, the VAP had no venous component at all, which was interpreted as reflecting decreased filling of the jugular veins. The estimated venous pressure also dropped at this time. Yuganov interpreted the drop in upper-body venous pressures during the second month of flight as indicating a new level of homeostasis that included completion of adaptative reactions of the venous circulation. The transient rise in jugular pressure would agree with impedance measurements, also collected on Salyut 4, indicating an initial increase in jugular venous pressure and filling followed by a decrease.[11] These findings are inconsistent with the American impression of a sustained dilation of the veins of the head and neck throughout the 84-day Skylab-4 mission and with the sustained elevation of jugular blood flow seen in two cosmonauts during Salyut-5[93] (see below).

On later Salyut-5 missions, rheography was used to estimate changes in the blood volume of the head, liver, and diaphragmatic section of the right lung.[93] As in most previous flights, head perfusion seemed to increase early during the flight, with marked edema and ruddiness of the face, headache, and estimations of elevated jugular venous- and pulmonary-artery pressures. The rheographic tracings indicated increased blood filling in the head early during flight and in the liver and right lung in the second month of the mission. The increases in lung and liver filling were interpreted as compensation by the venous circulation to the increased upper-body venous filling. In contrast to the impedance results described above,[11] rheographic estimates of jugular venous pressure remained stable during most of the flight and were interpreted as an incomplete adaptation of the circulatory system to weightlessness.

During an 8-day Salyut-7 mission, jugular diameter (measured by ultrasound) was considerably increased, and the waveform profiles of both jugular and femoral venous blood flow were markedly altered.[52,53] Before flight, jugular blood flow varied markedly during different phases of the cardiac cycle. During flight, these variations became dampened, suggesting increased blood flow. Femoral blood flow before flight was only weakly modulated by changes in breathing and heart rate; during flight, however, the flow pattern became much more variable. These responses were interpreted as differing effects of spaceflight on the venous pressures and resistances of upper- and lower-body veins, with upper-body venous pressures increasing and lower-body venous pressures decreasing. These investigators concluded that an increase in cardiac output, without significant increases in cerebral or femoral blood flows, is suggestive of increases in renal or hepatosplanchnic circulation during some phase of this relatively brief flight.[52,53]

2. *Postflight Results*

The Gemini missions included measurements of cardiovascular responses to 15 minutes of 70° head-up tilt before and after flight. Calf circumference in 10 Gemini crew members indicated consistently greater pooling of fluid in the lower extremities during tilt immediately after return to Earth; this pooling returned to normal within 50 hours of splashdown.[1]

Calf volume was measured in response to LBNP during and after Skylab missions.[61] LBNP-induced increases in calf volume at all pressure levels abruptly dropped on landing day from elevated in-flight levels to approximately preflight levels; on the first and second days after landing, the change in leg volume during LBNP was slightly greater than preflight values. The pattern of leg-volume response to LBNP also shifted: During flight, more than half of the change in volume had already occurred at the end of the –30 mm Hg LBNP stage, probably because the leg veins were relatively empty. However, after landing, changes in leg volume were greatest during the –40 and –50 mm Hg LBNP stages, presumably because a more intense negative pressure was required in the now filled vessels. The authors suggested that in-flight leg-volume responses at the less intense levels of LBNP reflect active venous constriction, which is attenuated after landing. Johnson and colleagues also observed that during preflight tests, leg volume returned to baseline level within 5 minutes of termination of the LBNP protocol. Leg volume recovery was delayed during flight, however, and remained "considerably delayed" in two crew members after the last and longest Skylab flight.

Venous-arterial pulsograms were obtained from two cosmonauts on the second Salyut-4 expedition 3 hours, 6 hours, and 3 days after landing.[11] At 3 and 6 hours after landing, the supine-resting pulsogram of both cosmonauts showed pulsations only from the carotid artery, and none from the jugular veins, suggesting a decreased filling of jugular veins and reduced jugular pressure. Similar results were observed in two of the four cosmonauts on the 18- and the 49-day Salyut-5 missions.[93] On the third day after Salyut-4, one cosmonaut's jugular pulsations and jugular pressure had returned to preflight levels (and orthostatic stability was regained); the other's venous pulsations had not. These postflight results agree with previous data from crews of shorter Salyut-3 missions and from the first crew of Salyut-4. Yuganov et al.[11] concluded that significant changes occur in the venous circulation during spaceflight and persist longer than do other hemodynamic indexes. Restoration of venous components of VAP and elevation of venous pressure on different days after flight were attributed to several readaption processes, including tonus of peripheral vessels, fluid-electrolyte balance, muscular activity, etc.[67,93,94]

C. Cerebral Vascular Responses to Weightlessness and Return to Earth

If normal autoregulatory mechanisms are perturbed, the general increase in upper-body perfusion during the first hours of flight could be accompanied by an increase in cerebral blood flow. This possibility has been investigated indirectly by using impedance rheography (Soviet) or a transcranial Doppler (TCD) device (U.S.). Middle cerebral-artery blood flow was monitored with a TCD device in eight crew members on two 1989 Shuttle missions to document cerebral-artery responses to spaceflight and to determine whether changes in cerebral blood flow might contribute to the development of space motion sickness. Significant changes in estimated cerebral vascular resistance were detected with the TCD during the first day of flight only in crew members not afflicted by space motion sickness; the sick individuals did not show this response (J. P. Bagian, personal communication).

Regional cerebral perfusion in Salyut-6, Salyut-7, and Mir crew members was investigated with a tetrapolar-impedance method.[24,60,75,87,88] During brief flights, no consistent changes were detected in blood filling and tone of cerebral vessels. However, during the longer flights, pulse blood filling in the left hemisphere decreased during the second through the eighth months of flight by 10%, resulting in a moderate asymmetry in blood filling of the two hemispheres. Cerebral rheograms also suggested decreased precapillary and postcapillary tone of small cerebral vessels; several other studies of venous waves indirectly indicated an impairment in venous outflow from the head region. Cerebral vasodilation of small vessels in the basin of the internal carotid arteries may have served to improve blood flow and prevent further venous congestion. These vascular reactions were thought to reflect adaptive reflex responses initiated from receptors in the cardiovascular region as a result of the increased central blood volume. Postflight impedance testing after a long Salyut-6 mission indicated attentuated cerebral pulse blood filling during head-down tilt (6 minutes at −15° followed by 6 minutes at −30°) relative to preflight measurements; this change did not resolve for approximately 5 weeks.[58] These changes were interpreted as a compensatory-adaptive response to counteract head over-filling during weightlessness.

Rheoencephalography (REG) also has been used to evaluate the effect of spaceflight on the reactivity of cerebral vessels during exercise or LBNP.[95] Before exercise or LBNP sessions, tone of the small vessels of the brain was higher and systolic blood filling 18% lower during Salyut-6 flights relative to preflight measurements. LBNP and exercise both decreased the stability of the rheoencephalogram in all cosmonauts tested, with the character of the response varying with length of flight. For example, cerebral perfusion decreased more at given levels of LBNP stress, and increased more at cessation of exercise, during flight relative to before. Before flight, REG indexes after an exercise bout tended to normalize within 3 to 7 minutes; after 53 to 60 days of flight, however, normalization frequently was not observed even 10 minutes after termination of the exercise.

Flight-related changes in cerebral circulatory function seem to persist for several weeks after prolonged flight. Kasyan et al.[95,96] noted that REGs recorded from four cosmonauts after the first and second Salyut-4 missions were distinctly different from those recorded before and during flight, as well as having distinct individual patterns. REG responses to LBNP and to exercise after flight were similar to those observed during flight.

IV. Carotid-Baroreceptor Cardiac Reflex Responses

The function of the carotid sinus-baroreceptor reflex was tested before and after STS-27 in December 1988.[97] Carotid baroreceptor areas were stimulated by application of stepped positive and negative pressure to a Silastic chamber applied to the anterior of the neck.[98] On landing day, R-to-R intervals, their standard deviations, and the operational point were all reduced relative to preflight findings. The first two measures provide a reliable estimate of efferent vagal-cardiac activity[99]; the latter finding reflects a loss of hypotensive buffering capacity due to vagal withdrawal. On the second postflight day, the slope and range of the R-to-R interval response curve were significantly less than before flight, and these reductions persisted through all subsequent postflight test days. In contrast, the operational point had recovered by the second postflight day.

Reductions in the operational point of the reflex response after flight were directly related to postflight reductions in the ability to maintain arterial pressure upon standing. In a backward elimination model, change in the operational point was the primary predictor ($P = 0.0041$) and change in body mass the second most important predictor ($P = 0.034$) of preflight-to-postflight changes in systolic pressure upon standing. The R value for the model was 0.64, $P = 0.0034$. In addition, a cluster analysis of systolic pressure responses to standing revealed two groups of subjects, one that was more resistant and one less resistant to the stress of standing on landing day. In the more resistant group, the average increase of systolic pressure with standing was 3 ± 2 mm Hg greater on landing day than before flight. In the less resistant group, the average increase in systolic pressure with standing was 17 ± 3 mm Hg less on landing day than before flight ($P = 0.0001$). The two groups also differed significantly in their postflight diastolic pressure responses to standing after flight (−0.9 ± 3.9 mm Hg vs −9.3 ± 4.6 mm Hg, $P = 0.031$), in the magnitude of postflight reductions in operational points (−6.9% ± 3.0% vs −30.8% ± 4.7%, $P = 0.0005$), and in the amount of mass lost during the flight (−0.8 ± 0.5 kg vs −1.44 ± 0.3 kg, $P = 0.0001$). (These group differences were not evident after landing day.)

Crew members in the group with smaller increases in systolic pressure during standing seemed to have two factors working against them. First, their operational points were much lower than those of the more resistant group. Thus, they had less capacity for early heart-rate speeding with standing, secondary to vagal withdrawal. Second, they lost more body mass (probably reflecting greater loss of fluid volume) after flight. Curiously, this group's impaired ability to maintain systolic pressure upon standing occurred despite a slightly greater cardioacceleration than that of the resistant group. This suggests that greater impairment of standing blood pressure responses may have resulted from factors other than heart rate, such as vasomotor function, total blood volume, or stroke volume.

Reduction in heart-rate response to carotid-baroreceptor cardiac-reflex function for up to 10 days after landing is consistent with data from Soviet missions[100,101] and with data from the U.S. Skylab missions,[61] which showed that sympathetic mechanisms were abnormal for up to 25 days after flight. These observed reductions also agree with bed rest data, which showed that subjects' baroreflex function had not returned by the fifth day of ambulation after a 30-day period of head-down bed rest (unpublished data).

V. Pulmonary Function

Few data are available regarding pulmonary function during acute adaptation to weightlessness. Pneumograms, part of standard monitoring during early spaceflights, included measures of respiration rate.[82] As would be expected from heart-rate responses during the first few hours of spaceflight, respiration rates tend to be high during launch and orbital insertion,[13,50,82,102,103] after which they stabilize at levels somewhat higher than preflight baselines.

Data regarding pulmonary function at rest during long missions are limited to measurements of respiration rates and vital capacities. In-flight resting respiration rates in eight cosmonauts during 30- to 175-day missions tended to be higher than preflight levels,[33] a finding consistent with an observed increase in resting heart rates during flight.

Vital capacity measured in 12 crew members during 59- to 175-day missions is shown in Fig. 13.[96,104] Although much

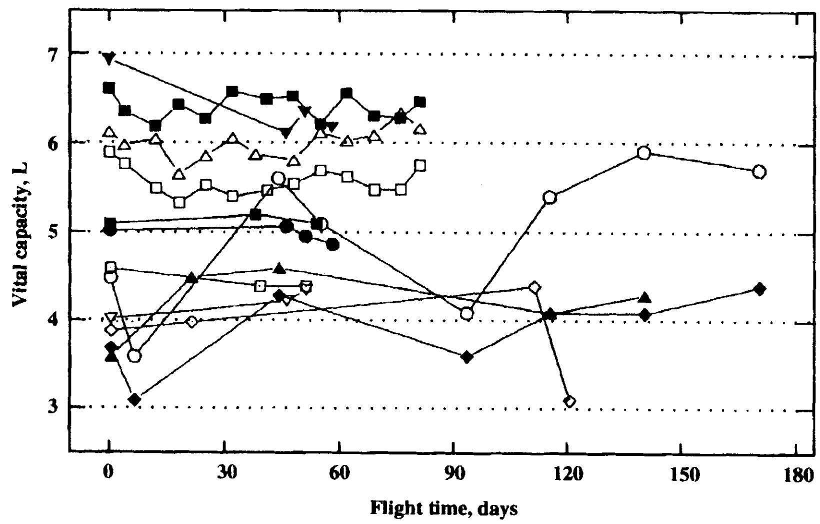

Fig. 13 Vital capacity in 12 crew members during 59- to 175-day flights.

variability exists between individuals, vital capacity seems to be reduced early in flight, and then tends to stabilize at or above preflight levels. Whether this effect can be attributed to fluid redistribution or to other factors (such as a reflection of the decrease in cabin ambient pressure to one third of sea-level pressure, as was the case aboard Skylab), is unknown. Most postflight measurements in this group fell within about 0.5 L of preflight values, although exceptions were noted after a short (8-day) flight and two long ones (140 and 175 days).[19,96,104] The reasons for these discrepancies are unknown, although the lack of in-flight countermeasures on the 8-day flight may have been a factor.

Postflight respiratory minute volume was 0.9 L/min less than preflight measurements in seven cosmonauts after 3- to 18-day flights; however, two subjects had larger volumes after landing (by 2.0 L/min and 1.6 L/min, respectively).[102]

VI. Responses to Provocative Tests

A. Orthostatic Stress

1. In-Flight Results

The diminished ability of the cardiovascular system to function effectively against gravitational stress upon return to Earth has been the primary cardiovascular consequence of spaceflight. Orthostatic intolerance is defined here as the inability of the cardiovascular system to maintain an adequate blood pressure when the upright posture is assumed. Orthostatic intolerance is manifested by actual or imminent syncope when cerebral blood flow is severely compromised. Milder forms of impaired orthostatic function are detected by exaggerated increases in heart rate and decreases in pulse pressure in response to orthostatic stress, and by the variable presence of presyncopal signs and symptoms such as lightheadedness, pallor, diaphoresis, and nausea. Evidence is presented here for the development of impaired orthostatic function during spaceflight.

Orthostatic tolerance was first tested in flight on Salyut-1 in 1971[105] with a "Chibis" lower-body negative-pressure (LBNP) device. All but one of the subsequent Soviet space station missions have carried a Chibis unit. Tolerance to LBNP has been evaluated during the first 2 weeks of some of these missions.[19,33,57,71,105–107] The mean in-flight heart rate and MAP responses in these populations were not significantly different from preflight responses (Fig. 14).

U.S. studies of orthostatic function in weightlessness began with the Skylab Program.[61] Skylab crew members recorded their heart-rate and blood-pressure responses to the orthostatic-like stress provided by an on-board LBNP device every 3 days during flight. The LBNP protocol consisted of five stages: 1 min at –8 mm Hg, 1 min at –16 mm Hg, 3 min at –30 mm Hg, 5 min at –40 mm Hg, and 5 min at –50 mm Hg. Heart-rate and blood-pressure responses were already exaggerated relative to preflight results by the first in-flight tests (on the fourth to sixth day of flight). Two of the nine crew members became syncopal during the last stage of the protocol on the fifth and sixth day of flight; a third became presyncopal at –40 mm Hg on the tenth day of flight. Resting heart rate reached plateaus after about 10 days of flight, and stressed heart rate after about 20 days.

Blood pressure generally was maintained throughout those LBNP tests that did not end in presyncope or bradycardia. The increase in heart rate was greater during flight than before, which could reflect compensation for a reduction in blood volume early in flight. Calf volume increases with LBNP were greater during flight than before, probably because greater volumes of blood were required to fill the relatively empty veins during flight. The contribution of other decrements in other elements of the orthostatic response, e.g., changes in baroreceptor-reflex responsiveness, were unknown.

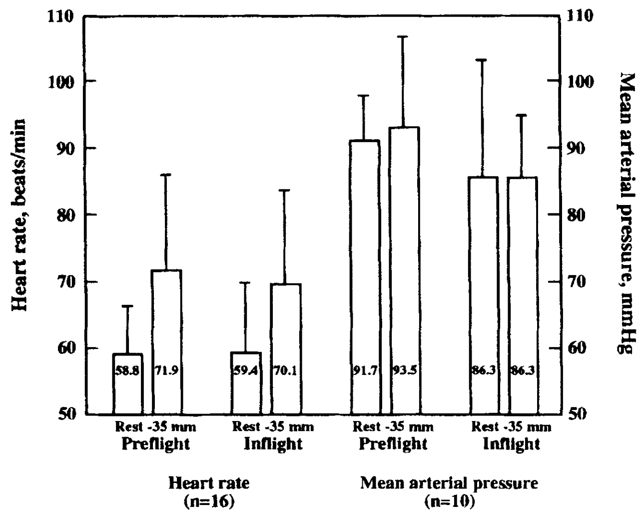

Fig. 14 Heart rate and mean arterial pressure responses to LBNP early in flight.

Responses to final in-flight LBNP tests were similar to and thus predictive of responses during the immediate postflight period. Although no progressive decrements in orthostatic responses were observed during the Skylab missions, the natural course of orthostatic dysfunction as a function of flight duration alone could not be determined on these flights. Skylab missions included regular in-flight exercise programs; also, greater emphasis was placed on hydration and nutrition during the second and third missions. Finally, the LBNP response test itself has been shown to improve orthostatic responses for as long as 24 hours after the test.[108]

LBNP protocols have been in effect during all but one of the missions to the Salyut and Mir space stations. The first Soviet LBNP test protocol had two stages: 2 min at –25 mm Hg and 3 min at –35 mmHg[109]; the present protocol has an additional 3-minute step at –45 mm Hg.[24,60] On the 30-day and 63-day missions to Salyut-4, tolerance tests were performed once a week.[110] Increases in heart rate in response to LBNP were greater during flight than before, except when LBNP was accompanied by ingestion of salt and water as a countermeasure on the last flight day.

Yegorov et al.[111] reported that responses to LBNP were more pronounced during all the 65- to 237-day missions than they were before flight: heart rate and peripheral resistance increased more, and left ventricular ejection time, vascular tone and muscle tone, and tissue and venous pressures decreased more. Gazenko et al.[109] concluded that this greater reactivity to provocative tests during flight resulted from the cardiovascular conditions before the test. They also reported that cardiovascular reactivity to provocative tests did not increase with time, which they interpreted as indicating that the cardiovascular systems of the crew members had adapted to weightlessness. Bogomolov et al.[15] reported that the in-flight responses of one cosmonaut to LBNP were similar to his responses before flight; they concluded that this man's cardiovascular system remained stable for the 326 days he spent in space. The individual responses of the crews to in-flight LBNP on 49-day and 17-day missions to Salyut-5 predicted postflight responses to orthostatic stress,[94] a finding that agrees with those from the Skylab Program.[61] Several crew members reportedly had no problem with LBNP during flight, and experienced no postflight orthostatic intolerance; one crew member showed decreased tolerance to LBNP starting on flight day 23, had two in-flight tests stopped by physicians, and experienced decreased orthostatic stability after flight.

The importance of blood volume to simulated orthostatic stress during flight was investigated by Grigoriev,[112] who observed that both crew members of the 63-day Soyuz-18 mission to Salyut-4 in 1975 tolerated in-flight LBNP tests better after consuming 4 g NaCl with about 1000 mL water. With the salt and water supplement, tachycardic heart-rate responses to –25 mm Hg and –35 mm Hg were fewer and pulse pressures were greater. Subsequently, it was recommended that all 10 Salyut-6 crew members consume 6–9 g NaCl in 900–1200 mL of water, exercise regularly, and use LBNP regularly during the final 2 to 5 days of the mission in order to enhance acceleration tolerance and prevent postflight orthostatic intolerance. Although no data were presented, Grigoriev concluded from postflight medical examinations that the combination of countermeasures had a noticeable beneficial effect on cardiovascular responses.

In-flight assessment of orthostatic responses was continued in the U.S. space program during selected Space Shuttle missions since January 1990. This investigation largely confirmed the Skylab findings of increased heart rate during LBNP, and demonstrated that this response is well developed even earlier in flight than previously observed.

2. *Postflight Results*

U.S. observations. Postflight orthostatic dysfunction was first suspected in U.S. astronauts after the 9-hour Mercury-8 mission[42] and then confirmed after the 34-hour Mercury-9 mission.[63] Subsequently, provocative tests of orthostatic function, such as head-up tilt, passive standing, and the use of LBNP, have become standard after all flights.

Imminent syncope was first observed after the Mercury-9 mission in 1963.[63] This astronaut's landing heart rate of 132 beats per minute while he lay in the spacecraft may have been related to taking dextroamphetamine in flight, but the rate increased by 42% (to 188 beats per minute) when he stood on the deck of the recovery ship. His blood pressures while in the spacecraft were 100/65 mm Hg and 105/87 mm Hg, but the automatic blood-pressure device detected no pressure pulses when he stood on the deck. After about 1 minute of standing, the astronaut became pale and diaphoretic, swayed slightly, and reported lightheadedness, dimming of vision, and tingling of the feet and legs. During tilt-table studies performed 1, 3, and 6.5 hours after landing, the astronaut's average heart rate during head-up tilt was 48% higher than while he was supine, in contrast to a 29% average increase with tilt during 11 preflight tests. Postflight blood-pressure responses to tilt were similar to those observed before flight, and no presyncopal symptoms were reported during the postflight tilt tests.

During the Gemini Program (1965–1966), hypotension was not apparent while crew members remained seated inside the spacecraft after landing, and no crew members reported presyncopal symptoms or syncope upon leaving the spacecraft.[1,2] Orthostatic problems were detected only during tilt-table tests,[2] and at least one crew member was syncopal during one of his tests (D. O. Coons, personal communication). Tilt-table tests performed after flight consistently evoked greater increases in heart rate (from 17% to 105%) and a greater narrowing of pulse pressures than preflight tests.[2] Abnormal tilt-table responses persisted for 48 to 50 hours after landing.[1,2]

Both graded LBNP tests and passive stand tests were used to evaluate orthostatic function during the Apollo Program; five crews were evaluated by LBNP tests only (n=18), two by stand tests only (n=6), and one by both methods (n=3).[29,30] During the first postflight LBNP tests, which were performed 2 to 7 hours after splashdown, one of the 18 crew members studied became presyncopal before –50 mm Hg of LBNP was reached; five others developed presyncopal symptoms at –50 mm Hg. Immediately after flight, the average increase in heart rate at –50 mm Hg was 57%, in contrast to 24% before flight. Blood-pressure changes were less pronounced; systolic pressure fell by 18% (10% decrease before flight), diastolic pressure remained essentially unchanged (6% increase before flight), and pulse pressure narrowed by 45% (31% narrowing before flight). During the second postflight tests (usually performed 24 hours after splashdown), a different crew member became presyncopal before reaching –50 mm Hg. During the third postflight tests (usually performed 48 hours after splashdown), only 15 of the 18 crew members participated, but all tolerated the full test. Blood-pressure responses had returned to their preflight levels by 24 hours, but the heart-rate response was still slightly greater than before flight at the final LBNP test.

The increased heart-rate response to passive standing after flight during the Apollo Program paralleled that observed during the LBNP tests, but narrowing of the pulse pressure was the result of an increased diastolic pressure rather than a fall in systolic pressure as observed during LBNP tests. From the combined LBNP and stand test data, Hoffler and Johnson[30] found a statistically significant correlation of 0.52 between the percent change in resting heart rate after flight and the percent change in orthostatically stressed heart rate after flight.

After Skylab missions, postflight orthostatic intolerance was no more severe than it had been after shorter missions, but a longer time was required for orthostatic responses to return to preflight levels.[61] In fact, the most pronounced responses to LBNP after Skylab missions often occurred several days after landing rather than on landing days.

Although Skylab results suggested that decrements in orthostatic function on orbit may reach a point of stabilization after several weeks, new concerns about orthostatic intolerance arose during Shuttle flights. Specifically, crew members experience the acceleration force along the Gz (head-to-foot) axis of the body, with loads as high as 1.5 *g* to 2.0 *g* when piloting and landing the orbiter. Crew members of all previous U.S. spaceflights and nearly all Soviet space missions have returned ballistically, experiencing the acceleration force along the Gx (chest-to-back) axis of the body. Exceptions were crew members of the six Vostok missions, who ejected from the capsule, completing the final few minutes of return by individual parachute.

The passive stand-test was resumed as the provocative technique for evaluating postflight orthostatic function in the Space Shuttle Program. Passive standing after the first four test flights, which lasted 2 to 8 days, produced an average 22.1% increase in heart rate, a 3.0% decrease in systolic pressure, a 1.5% increase in diastolic pressure, and an 11.0% decrease in pulse pressure. One crew member developed presyncopal symptoms after flight. Although no presyncopal symptoms have been reported to interfere with landing the Space Shuttle, symptoms or actual syncope during either egress or postflight orthostatic tests have been observed 8 times during the first 26 missions (unpublished data).

Heart-rate increases during postflight orthostatic tests peaked after flights of 8 days and were less after flights of 12 to 14 days.[113] The ingestion of salt tablets and water before landing simply shifted the heart-rate curve downward. Furthermore, the cardiothoracic ratio, measured from an X-ray film,[114] was reduced after flights lasting 3 days but did not differ from preflight values after flights lasting 12 and 14 days. These investigators concluded that loss of orthostatic tolerance and "heart size" are multiphasic processes having physiological mechanisms that vary with time, and that the loss of body-fluid volume is only one component of postflight orthostatic intolerance.

Standardized measures of orthostatic function have been difficult to obtain and interpret for several reasons. First, initial testing invariably takes place after minutes to hours of readaptation, during which crew members can stand and walk. Ad lib intake of fluid and use of G-suits after landing also confound results. Furthermore, attention to hydration is variable in flight, and the operational end-of-mission fluid-loading countermeasure is not always performed consistently with respect to timing or the volume or tonicity of the fluid consumed. In the future, orthostatic responses may be monitored in the Shuttle from the time of reentry through cabin egress after landing.

Soviet/Russian observations. Passive tilt tests are performed routinely before and after Soviet/Russian flights as well. The last three Vostok pilots experienced a greater heart-rate increase during the test after flight than before, and heart-rate recovery was prolonged.[62] Two of the three Voskhod crew members experienced 26% to 47% reductions in stroke volume and cardiac output in response to the test 24 hours after landing, a greater response than that before flight.[44] Seven of 11 crew members on early 2- to 5-day Soyuz missions, and two on an 8-day flight, showed a greater postflight heart-rate response to passive tilt.[115]

Postflight orthostatic intolerance was unexpectedly severe after the Soyuz-9 mission. During the 18-day flight, the cosmonauts exercised daily for two 1-hour sessions consisting of mainly upper-body training using a chest expander and donning a prototype treadmill harness to provide an axial load on the body[116]; no other countermeasures were used. For the first 3 hours after landing, the crew members' attempts at standing were accompanied by lightheadedness, weakness, and tachycardia to the point where they preferred to remain supine. Heart rate and blood pressure were measured while crew members were supine, sitting, and standing within 2 hours after landing.[117] Both cosmonauts responded with facial pallor. Seated heart rates increased by 33% and 22%, and pulse pressure narrowed by 50% and 43%. Standing heart rates increased by 63% and 65%. Korotkoff sounds were not detectable in one cosmonaut as he stood and were audible only once in the other, at which time pulse pressure was reduced by 71%. These responses were much greater than those observed before flight, but resolved within a few days.

On subsequent missions of equal or longer duration, in-flight countermeasures such as regular exercise on a bicycle and a treadmill (see below), oral saline-loading, and LBNP training before landing have reduced the severity of postflight orthostatic intolerance. Although orthostatic function impairments are greater after flight than before, no correlations are apparent in their severity or duration with time spent in flight. For example, postflight orthostatic intolerance in a cosmonaut who completed an 11-month mission was no greater than that of his fellow crew members who flew for 6 months, or of other cosmonauts after shorter missions.[15]

B. Exercise

1. In-Flight Results

EVAs have consistently provoked increases in heart and respiration rates, probably from the combination of physical exertion and emotional stress. Cosmonauts aboard both Voskhod missions reported increased fatigue and a tendency to perspire in response to moderate physical activity during these one-day flights. The pulmonary ventilation of the Voskhod-2 cosmonauts reportedly increased more than twofold during that flight, which included the first EVA.[44] The heart rate of one of these cosmonauts increased steadily from about 110 beats per minute to a maximum of 168 beats per minute[44] while he was trying to reenter the spacecraft's air lock. By comparison, a Gemini-4 crew member's heart rate was 140 beats per minute while he stood in the open hatch, and continued to increase during the EVA to a maximum 178 beats per minute when he reentered the spacecraft.[1]

Cardiovascular responses to an in-flight exercise device were evaluated on several of the Gemini missions.[2] In the first study, the load consisted of one pull per second for 30 seconds on a bungee device, for which the force at full extension equalled 160 kg. This test revealed no decrement in the heart-rate response after as many as 14 days in the spaceflight environment.

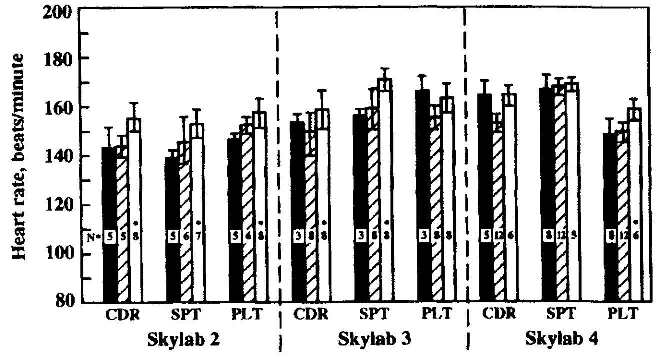

Fig. 15 Heart rates at 75 percent maximum exercise before (black bars), during (hatched bars), and after (clear bars) the three Skylab flights. CDR, commander; SPT, scientist pilot; PLT, pilot. Bars indicate standard deviation; *significantly different from baseline, P<0.05.

During the 8-month mission to Salyut-7, two cosmonauts who recorded their echocardiograms during LBNP also recorded their echocardiograms during a graded in-flight bicycle-exercise protocol. Both at rest and during exercise, LVEDV, stroke volume, and cardiac output were lower during flight than before. However, the ratio of left ventricular filling to stroke volume remained constant, indicating no decrease in myocardial contractility, but the ejection fraction and the velocity of circumferential myocardial fiber shortening were somewhat greater during exercise in flight than during preflight tests.

Studies aboard Skylab and Salyut-6 demonstrated that exercise capacity is not adversely affected in flight.[57,107,118] Heart rates in Skylab crew members during 75% maximum exercise before, during, and after flight are shown in Fig. 15. The heart rates of most of these men were higher during exercise after flight than before, but were little different during in-flight exercise. Similarly, measures of oxygen sufficiency in Salyut cosmonauts showed no change in performance under physical load (i.e., exercise) during flight.

During the second primary expedition to Mir, cosmonauts exercised on a motorless treadmill in four stages ranging from walking to a fast run.[15] The cosmonaut who flew the entire 326-day mission experienced progressively smaller increases in heart rate in response to increasing loads during flight, and his heart-rate response 3 to 4 months into the mission was less than that observed before flight. However, another cosmonaut was unable to complete the test on flight day 84 because he developed a heart rate greater than 200 beats per minute with unspecified extrasystoles at a slow run. The response of this cosmonaut to exercise reportedly improved during later tests. The third cosmonaut apparently showed no change in exercise capacity.

2. Postflight Results

Measures of cardiopulmonary responses to exercise after spaceflight have consistently revealed declines in exercise capacity. Five of six Gemini crew members exhibited a decrease in exercise capacity, as determined by heart-rate response and a reduction in oxygen consumption to a quantified workload.[2]

Early in the Soyuz program, cardiovascular and respiratory responses to submaximal physical loads were studied after flight by using a bicycle ergometer. After landing, cosmonauts had greater increases in heart rate and greater decreases in oxygen pulse, without substantial changes in oxygen consumption, than during the preflight period. The elimination of CO_2 increased, and four of seven cosmonauts studied subjectively felt greater stress under the physical load. Hemodynamically, increases in the maximum and mean arterial pressure, and decreases in the minimum arterial pressure, tended to be greater after performing a physical task.[13]

Measurements also were obtained before and after flight on Apollo 7 through Apollo 11.[119] These studies demonstrated significant decreases immediately after flight in workload, oxygen consumption, systolic blood pressure, and diastolic blood pressure at a heart rate of 160 beats per minute. Mechanical efficiency (i.e., the oxygen required to perform a given amount of work) showed no gross changes after flight. Studies of Skylab crew members revealed similar postflight decrements in exercise capacity, evidenced by decreases in oxygen uptake, pulse, cardiac output, and stroke volume.[118] Most of the cardiovascular responses returned to normal within 3 weeks.

Crew members of the longer missions in both programs did not require more time for readaptation after flight. Readaptation time did not vary substantially after Soviet missions lasting 96, 140, 175, or 185 days. All cardiovascular variables returned to normal within 18 to 21 days for the Skylab-2 crew (28-day mission), 5 days for the Skylab-3 crew (59-day mission), and 4 days for the Skylab-4 crew (84-day mission). Since the crew of Skylab-4 exercised the most during flight and the crew of Skylab-2 the least, the amount of exercise performed in flight seems to be inversely related to the amount of time required for the cardiovascular system to readapt to Earth. Of course, factors other than the amount of in-flight exercise may have contributed to this apparent paradox. For example, high initial levels of conditioning may be a factor, especially if the vigorous in-flight exercise required to maintain this level of conditioning is not performed. Loss of muscle mass might also contribute to this phenomenon, since significant losses and decreased strength will result in early fatigue and inability to complete the stress-test protocols.

VII. Summary and Conclusions

Human excursions into space have revealed that the cardiovascular and cardiopulmonary systems adapt promptly and apparently satisfactorily to weightlessness. However, these adaptations are no longer appropriate when the crew returns to Earth, and variable periods are required to recover preflight function. Virtually all space travelers have experienced some degree of orthostatic dysfunction upon return to Earth. Since the resumption of Space Shuttle flights in 1988, the percentage of crew members with signs and symptoms of orthostatic dysfunction when they first stand in the vehicle, or during passive stand tests immediately after flight, has been greater than expected, despite the use of a fluid-loading countermeasure.

In the U.S. space program, most of the biomedical investigations into the human health effects of spaceflight have been assessments of the status of crew members after flight in relation to their preflight status. Although valuable, these data have left unknown the time course and physiological mechanisms by which decrements in cardiovascular function develop. The Soviet space program has provided more opportunities for in-flight studies during long-duration flights, but the same deficiencies exist in the data.

To date, orthostatic dysfunction has not posed an operational hazard to returning astronauts and cosmonauts during entry and landing maneuvers, but the potential exists nevertheless. The question of whether fully suited Space Shuttle crew members are able to perform an emergency egress, given the almost universal presence of some degree of orthostatic dysfunction, is currently being evaluated.

Performing formal tests of orthostatic function after the initiation of activities that are known to restore impaired orthostatic function (ambulation and rehydration) has made it impossible to provide a credible estimate of the risk of orthostatic intolerance and dysfunction during the actual entry, landing, and egress sequence of Space Shuttle missions. Both Soviet and U.S. investigations have failed to account for the effects of potential confounding variables. A further problem common to both programs is the implementation of countermeasures before the basic physiological phenomena have been understood. Use of several countermeasures simultaneously also has interfered with independent assessments of each countermeasure. Moreover, changes in physiological variables in response to spaceflight have not been assessed with regard to age, gender, initial body mass, etc.

Recently the U.S. began a new series of investigations designed to address the medical consequences of atmospheric reentry, landing, and egress from the Space Shuttle after crew members have been in flight for up to 16 days. Although the duration of these anticipated flights is relatively short compared to space station missions, crew members experience acceleration forces along the head-to-foot axis of the body when piloting and landing the vehicle. Thus, medical problems that previously posed no risk to returning astronauts might now affect crew safety. In particular, appropriate cardiovascular responses to orthostatic stress are essential. Marked presyncopal symptoms and frank syncope could seriously or completely impair the crew's performance during required cognitive and psychomotor activities during entry, landing, and egress after extended-duration missions.

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